

PATENT  
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IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicants: GRUE-SØRENSEN et al.

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Group: 1616

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For: THERAPEUTIC USE OF VITAMIN D ANALOGUES

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

I, Klaus Nielsen, do declare and say as follows:

1. I graduated as an MD in 1986 from the University of Copenhagen, Denmark and was employed as a physician at University Hospital Rigshospitalet, Copenhagen in department of Hepatology from 1987 to 1992. From 1994 to 2001 I have been employed by LEO Pharma A/S

in the Medical Department being Group manager in Nephrology. I have been in the Department of Business Development as a Chief Scientific Officer since 2002.

2. I am as a Chief Scientific Officer at LEO Pharma A/S experienced in evaluating new therapeutic approaches related to osteoporosis and am due to my previous positions well acquainted with nephrology and renal diseases such as hyperparathyroidism.

3. The bone related disease state seen in connection to hyperparathyroidism (caused by a raised level of parathyroid hormone) is not equivalent to the disease state of osteoporosis and related bone conditions. A correct description of the bone related disease caused by hyperparathyroidism is not osteoporosis but osteomalacia (or renal osteodystrophy when due to secondary hyperparathyroidism). Osteoporosis not only arises due to other causes, such as a combination of genetic, dietary, hormonal, age-related, and lifestyle factors, than osteomalacia caused by hyperparathyroidism, but more importantly, osteoporosis and osteomalacia differ in their symptoms. The term osteoporosis is sometimes erroneously used too widely in the literature and thus sometimes being confusingly and wrongly used also to cover the bone changes seen in connection to hyperparathyroidism. However, the bone related disease state caused by hyperparathyroidism can from a scientific point of view not be described as osteoporosis.

4. Due to the different etiologies between osteomalacia caused by hyperparathyroidism and osteoporosis, the two diseases are treated differently. The treatment of osteomalacia or renal osteodystrophy is achieved by the suppression of parathyroid hormone. Osteoporosis is not treated by suppression of parathyroid hormone, but by changing of the balance between anabolic and catabolic processes in the bone by targeting these processes directly e.g. by the use of bisphosphonates inhibiting bone resorption. Actually new treatment approaches in osteoporosis includes parathyroid hormone injection. In the present patent application the classic *in vivo* models for osteoporosis (ovariectomized rats – with normal parathyroid hormone levels) are used showing that the compounds surprisingly have such direct effects on the bones.

5. To further stress that osteoporosis is not a disease caused by increased level of parathyroid hormone, the FDA guidelines {CDER Document for Guidance: Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis (Issued 4/1994, Posted 2/18/1998)} do thus not accept the suppression of parathyroid hormone as a

surrogate parameter for the efficacy of a new osteoporosis compound. Data regarding the bone quality, such as bone mass, bone strength, and bone architecture, including the models of the present application are required by the FDA in order to get a compound approved for the treatment of osteoporosis and related bone disorders.

6. In view of the above, I conclude that it is not obvious to expect beneficial results for treating osteoporosis by using compounds which are effective against hyperparathyroidism.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.



Klaus Nielsen, MD

Date: 26 May 2004